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NEOADJUVANT CONCURRENT CHEMORADIOTHERAPY IN PATIENTS OF ESOPHAGUS AND GASTROESOPHAGEAL JUNCTION CANCER (SINGLE INSTITUTE STUDY)

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Abstract:

Background: Esophageal cancer and cancers of the gastroesophageal junction pose significant clinical challenges due to their aggressive nature and often late-stage diagnosis. Neoadjuvant concurrent chemoradiotherapy (CRT) has emerged as a pivotal therapeutic strategy in the management of locally advanced disease. By combining chemotherapy with radiation therapy before surgical intervention, neoadjuvant CRT aims to reduce tumor burden, increase resectability rates, addresses micro metastasis and improve overall survival outcomes.

Objectives: To evaluate pathological response after administering neoadjuvant chemoradiotherapy in patients diagnosed with esophageal cancer and cancers located at the gastroesophageal junction (Squamous cell carcinoma and Adenocarcinoma).

Materials and Methods: In this prospective interventional study, we enrolled a total of 36 patients, with a diagnosis of esophageal carcinoma or carcinoma of the gastroesophageal junction aged 18-70 years. The study duration was 6 month from (July 2023 to Jan 2024) and was conducted in Department of Radiation Oncology, National University of Medical Sciences (NUMS) Tertiary care Hospital Rawalpindi. During neoadjuvant chemoradiotherapy, patients received intravenous weekly carboplatin (AUC 2 mg/mL per min) and paclitaxel (50 mg/m²) starting on days 1, 8, 15, 22, and 29. Concurrently, radiation therapy was administered with a total dose of 41.4 Gy delivered in 23 fractions of 1.8 Gy per fraction over 5 days per week (excluding weekends).The entire neoadjuvant treatment spanned at 31 days, with treatment sessions held 5 days per week for the initial four weeks, and then reduced to 3 days in the fifth week. Then all the patients underwent surgery within 12 weeks of completion of the chemoradiation. At follow up we documented pathological responses as ypTx and ypNx cateogories as per American Joint Committee on Cancer (AJCC) 8th Edition.Histological

regression as compelete response, partial response and No response and types of resection as R0: no residual tumor, R1: microscopic residual tumor and R2: macroscopic residual tumor. A predesign questionere was used to collect data.

Results: The mean age of all 36 patients was 55.22±8.95 years. Clinical Stage as per AJCC 8th Edition showed no cT0 patients, 1 (2.8%) as cT1, 8 (22.2%) as cT2, 23 (63.9%) as cT3, and 4 (11.1%) as cT4; cN categories were 10 (27.8%) as cN0, 15 (41.7%) as cN1, 11 (30.6%) as cN2, and none as cN3. Gender distribution included 22 males (61.1%) and 14 females (38.9%). Age groups were 2 (5.6%) aged 18-40, 8 (22.2%) aged 41-50, 18 (50.0%) aged 51-60, and 8 (22.2%) over 60. Histological types were 10 (27.8%) adenocarcinoma and 26 (72.2%) squamous cell carcinoma. Pathological responses were 15 (41.7%) ypT0, 5 (13.9%) ypT1, 7 (19.4%) ypT2, 8 (22.2%) ypT3, and 1 (2.8%) ypT4; ypN categories were 20 (55.6%) ypN0, 8 (22.2%) ypN1, 6 (16.7%) ypN2, and 2 (5.6%) ypN3. Histological regression showed 2 (5.6%) with no response, 17 (47.2%) with partial response, 15 (41.7%) with complete response, and 2 (5.6%) not assessed. Most tumors were esophageal (32, 88.9%) versus gastroesophageal junction (4, 11.1%). Tumor resections revealed that 66.7% were R0 resections, R1 resections accounted for 25.0%. Lastly, 8.3% of the cases were R2 resections. Stratification by gender, age, and histological type showed no significant differences (p-values 0.11, 0.81, and 0.55, respectively).

Conclusion: Neoadjuvant concurrent chemoradiotherapy appears to be an effective treatment strategy for patients with esophageal and GEJ cancer, with promising pathological complete response which is likely to be a predictor of improved overall survival (OS).

Key words: Neoadjuvant concurrent chemoradiotherapy, Esophageal and gastroesophageal junction, Squamous cell carcinoma.

INTRODUCTION: Esophageal and gastroesophageal junction (GEJ) cancers pose a significant global health challenge, characterized by unfavorable prognosis and elevated mortality rates.(1, 2) These cancers often remain undetected until reaching advanced stages, contributing to complex treatment scenarios and diminished survival prospects.(3) Neoadjuvant concurrent chemoradiotherapy (NACCRT) has emerged as a standard therapeutic regimen aimed at enhancing surgical outcomes and prolonging survival among patients with these malignancies. This approach entails administering chemotherapy and radiotherapy prior to surgery, with the goal of shrinking tumors, facilitating their operability, and improving overall survival rates. Esophageal cancer ranks as the seventh most prevalent cancer globally and the seventh leading cause of cancer-related deaths.(4) In 2020, there were about 604,100 new cases and 544,076 deaths worldwide, with incidence rates varying widely by region, notably high in Eastern Asia, Eastern Europe, and parts of Africa.(5) In Pakistan, esophageal cancer poses a significant public health challenge, with incidence and mortality rates among the highest globally, especially in rural areas.(6) Factors such as tobacco use, hot beverages consumption are associated risk factors, although detailed national cancer registries remain limited.(7) NACCRT has been shown in multiple studies to improve outcomes for esophageal and GEJ cancer patients. A pivotal trial by van Hagen et al. (8) illustrated its superiority over surgery alone. In this randomized controlled trial involving 366 patients, those who underwent NACCRT followed by surgery achieved significantly higher rates of complete resection (R0 resection) and improved overall survival compared to those treated with surgery alone.

This study intended to replicate the initial landmark studies in patients reporting to our clinics. The role of Neoadjuvant chemoradiotherapy in local patient population will be tested.

Objective:

To evaluate pathological response after administering Neoadjuvant chemoradiotherapy in patients diagnosed with esophageal cancer and cancers located at the gastroesophageal junction (Squamous cell carcinoma and Adenocarcinoma).

MATERIALS AND METHODS:

Study Design: Prospective interventional study.

Study setting: Radiation Oncology, National University of Medical Sciences (NUMS) Tertiary care Hospital Rawalpindi.

Duration of the study: Duration of the study was 6 month ((July 2023 to Jan 2024)).

Sample Technique:

• Non-probability Consecutive sampling technique.

Inclusion Criteria:

- Biopsy Proven Squamous cell and Adenocarcinomas of Esophagus and Gastro esophageal junction.
- ECOG PS 0 and 1.
- Patients of age 18-70 years.
- Patients with locally advanced disease (typically stage II or III) as per the American Joint Committee on Cancer (AJCC) staging system or other relevant staging systems.
- Both male and female patients.

Exclusion Criteria:

- Patients having history of chemotherapy and radiotherapy to chest.
- Individuals who have experienced a reduction in body weight exceeding 10% of their initial weight.
- Patients with previous or ongoing history of cancer, excluding esophageal malignancy.
- Pregnancy.

Methods:

Following the approval of the synopsis by the ERC, all patients with esophageal and gastroesophageal cancer who presented to the Radiation Oncology Department at National University of Medical Sciences (NUMS) Tertiary care Hospital Rawalpindi were included in the study. The inclusion and exclusion criteria were strictly adhered to. A total of 36 patients were enrolled, and informed consent was obtained from the patients or their guardians after explaining the purpose of the study in their native language. All patients underwent clinical examination to ensure that they met the selection criteria. All patients underwent a planning computed tomography (CT), which was performed on Canon (AQUILION LB 16 slice) in the supine treatment position. The ECLIPSE 16.1 version treatment planning software (Varian) was used for contouring and treatment planning. Radiation therapy was delivered through VMAT technique. All treatments were delivered using 6MV Photons from a Varian CLINAC-DHX, to a total radiation dose of 41.4 Gy in 23 fractions @ 1.8 Gy/day over 5 days per week (excluding weekends), beginning simultaneously with chemotherapy. All patients received carboplatin (AUC 2 mg/mL per min) and paclitaxel (50 mg/m² of body-surface area) intravenously for five cycles, starting on days 1, 8, 15, 22, and 29 concurrently, with radiation therapy. The treatment lasted for 23 days, 5 days per week with Saturdays and Sundays off.

If the white blood cell count dropped below 1.0×10^9 cells per L or the platelet count fell below 50×10^9 per L on days 8, 15, 22, or 29, neoadjuvant chemotherapy was postponed by one week until recovery beyond these thresholds. Furthermore, if mucositis with oral ulcers or prolonged vomiting despite antiemetic premedication occurred, Chemotherapy was delayed by one week. Subsequent chemotherapy was halted if febrile neutropenia (defined as a neutrophil count $<0.5 \times 10^9$ cells per L and a body temperature >38.5°C), sustained creatinine clearance below 50% of the pretreatment level, symptomatic cardiac arrhythmia or atrioventricular block (excluding first-degree atrioventricular block), or other severe organ toxicity at grade 3 or worse (except for esophagitis) was present. Laboratory evaluations, including complete blood cell counts and serum creatinine measurements, were conducted weekly during neoadjuvant chemoradiotherapy, while radiological assessments were performed as needed. Patients were scheduled for surgery within 4–6 weeks after completing chemoradiotherapy. Pathological tumor response was assessed following surgery. A predesigned questionere was used to collect the data. SPSS (Version 25.0) was used for statistical analysis.

RESULTS:

The mean age of the 36 patients was 55.22±8.95 years. Patients, were clinically staged as per AJCC 8th edition was categorized into different cT and cN categories. One patient (2.8%) was categorized as cT1, while 8 patients (22.2%) were classified as cT2. The majority of patients, 23 (63.9%), were in the cT3 category, and 4 patients (11.1%) were classified as cT4. Regarding the cN category, 10 patients (27.8%) were categorized as cN0. The cN1 category included 15 patients (41.7%), while 11 patients (30.6%) were classified as cN2. No patients were classified as cN3 (0.0%). Out of 36 enrolled patients, there were 22 males (61.1%) and 14 females (38.9%). The age groups were distributed as follows: 2 patients (5.6%) were aged 18-40 years, 8 patients (22.2%) were aged 41-50 years, 18 patients (50.0%) were aged 51-60 years, and 8 patients (22.2%) were over 60 years old. Regarding histological type, 10 patients (27.8%) had adenocarcinoma, while the majority, 26 patients (72.2%), were diagnosed with squamous cell carcinoma. In terms of pathological response, for the ypT category, 15 patients (41.7%) were classified as ypT0, 5 patients (13.9%) as ypT1, 7 patients (19.4%) as ypT2, 8 patients (22.2%) as ypT3, and 1 patient (2.8%) as ypT4. The ypN category showed that 20 patients (55.6%) were classified as ypN0, 8 patients (22.2%) as ypN1, 6 patients (16.7%) as ypN2, and 2 patients (5.6%) as ypN3.

Histological regression was observed with 2 patients (5.6%) showing no response, 17 patients (47.2%) showing a partial response, and 15 patients (41.7%) showing a complete response, while 2 patients (5.6%) were not assessed. Additionally, 32 patients (88.9%) had esophageal tumors, and 4 patients had tumors at the gastroesophageal junction. Tumor resections revealed that 23 patients (66.7%) had R0 resections, 9 patients (25.0%) had R1 resection and 3 patients(8.3%) had R2 resections. The stratification of histological regression among patients reveals distinct patterns based on gender, age group, and histological type were shown in table 4 with insignificant p-value.

Table 1: Mean age of all enrolled Patient *(n=36)*

Variables	**Mean±SD**
Age (Years)	55.22±8.95

Table 2: Clinical Stage of all the enrolled patients *(n=36)*

Clinical Stage	Frequency	Percentage
cT category†		
cT0	0	0.0%
cT1	1	2.8%
cT2	8	22.2%
cT3	23	63.9%
cT4	4	11.1%
cN category†		
cN0	10	27.8%
cN1	15	41.7%
cN2	11	30.6%
CN3	0	0.0%

Table 3: Characteristics of all the enrolled patients *(n=36)*

Gender	Frequency	Percentage
Male	22	61.1
Female	14	38.9
Age groups		
18-40 years	2	5.6
41-50 years	8	22.2
51-60 years	18	50.0
>60 years	8	22.2
Histological type		
Adenocarcinoma	10	27.8
Squamous cell carcinoma	26	72.2
Pathological Response		
ypT category†		
ypT0	15	41.7
ypT1	5	13.9
ypT2	7	19.4
ypT3	8	22.2
ypT4	1	2.8
ypN category†		
ypN0	20	55.6
ypN1	8	22.2
ypN2	6	16.7
ypN3	2	5.6
Histological regression		
No response	2	5.6
Partial response	17	47.2
Complete response	15	41.7
Not assessed	2	5.6
Tumor location		
Esophageal tumor	32	88.9
Gastroesophageal junction tumor	4	
Tumor resections		
R0 resection	24	66.7
R1 resection	9	25.0
R2 resection	3	8.3

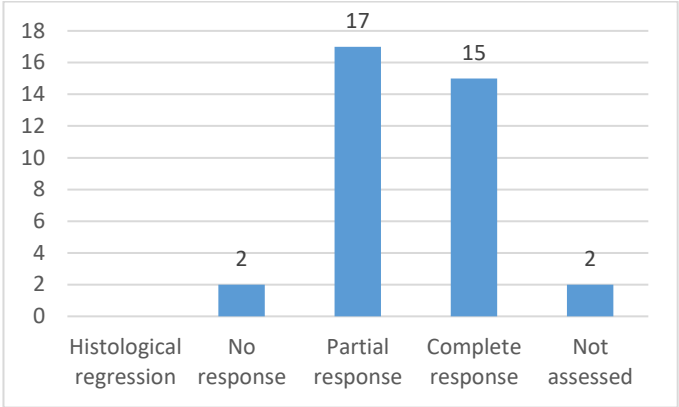

Fig 1: Frequency of Histological regression

Table 4: Stratification of Histological regression with respect to various variables *(n=36)*

	Histological regression				P-value
	Complete response	No response	Partial response	Not assessed	
Gender					
Male	6(40.0%)	1(50.0%)	13(76.5%)	2(100.0%)	0.11
Female	9(60.0%)	1(50.0%)	4(23.5%)	0(0.0%)	
Age group					
18-40 years	1(6.7%)	0(0.0%)	1(5.9%)	0(0.0%)	
41-50 years	5(33.3%)	0(0.0%)	3(17.6%)	0(0.0%)	
51-60 years	7(46.7%)	1(50.0%)	8(47.1%)	2(100.0%)	0.81
>60 years	2(13.3%)	1(50.0%)	5(29.4%)	0(0.0%)	
Histological type					
Squamous cell carcinoma	10(66.7%)	1(50.0%)	14(82.4%)	1(50.0%)	
Adenocarcinoma	5(33.3%)	1(50.0%)	3(17.6%)	1(50.0%)	0.55

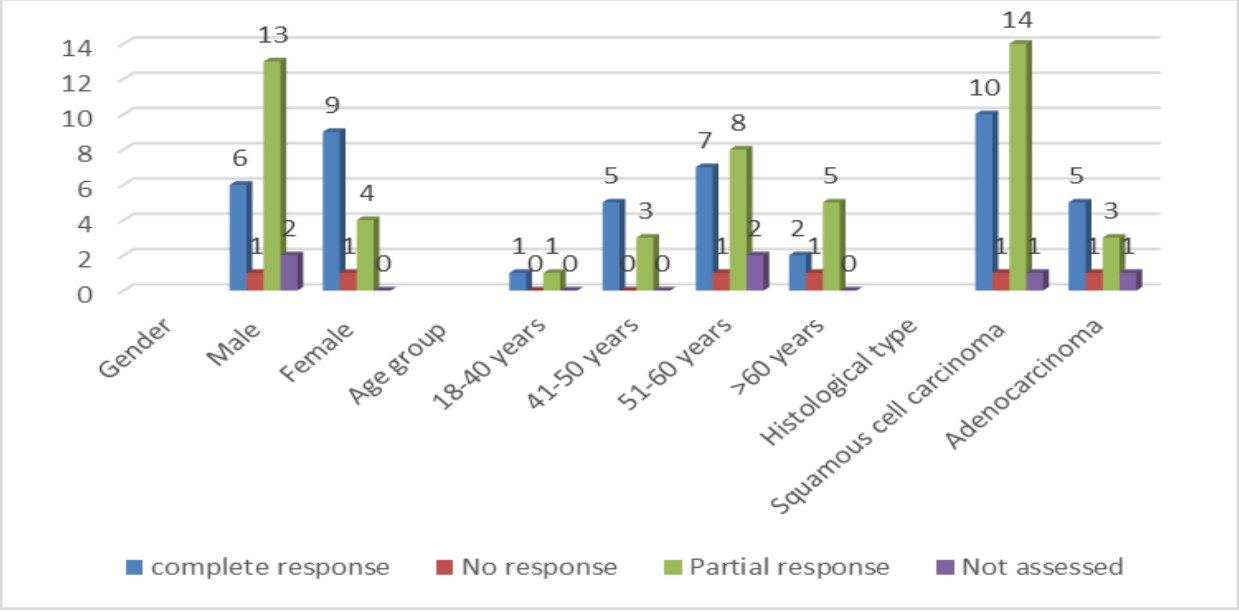

Fig 2: Stratification of Histological regression on the basis of various variables

Discussion: The use of neoadjuvant chemo radiation for locally advanced esophageal and gastroesophageal junction (GEJ) cancer is well-recognized.(9) This approach has shown to improve tumor down staging, achieve higher rates of R0 resection, address subclinical disease early, and enhance survival rates, all while maintaining a low incidence of severe adverse events. Neoadjuvant concurrent chemoradiotherapy (CRT) has become pivotal in the comprehensive treatment of esophageal and gastroesophageal junction (GEJ) cancer, presenting substantial therapeutic advantages and evolving treatment strategies. This method entails the administration of chemotherapy and radiation therapy before surgery, aiming to enhance treatment outcomes through effective local disease management, tumor size reduction, and potentially facilitating complete surgical removal (R0 resection).

The study assessed histological regression in patients with esophageal and gastroesophageal junction tumors, grouping their responses into four categories: no response, partial response, complete response, and not assessed. Two patients (5.6%) experienced no histological regression, suggesting that the treatment was ineffective, possibly due to underlying factors such as tumor biology or individual patient characteristics. Seventeen patients (47.2%) showed partial regression, meaning that while some cancer cells were eliminated, the treatment did not achieve full remission, indicating a moderate level of effectiveness. In contrast, fifteen patients (41.7%) experienced complete regression, with no remaining cancer cells detectable, highlighting the treatment's high efficacy and its association with a more favorable prognosis. Two patients (5.6%) were not assessed, likely due to insufficient tissue samples, which may have slightly affected the overall results. The majority of the tumors were located in the esophagus (88.9%), with the remainder at the gastroesophageal junction, underscoring the study's primary focus on esophageal cancer. These findings align with existing research that underscores the variability in treatment response based on tumor location and biology, as well as the critical importance of achieving complete regression for improved patient outcomes. Our study finding was supported by the study conducted by Maria Inês Vaz do et al.(10) Another study conducted by Alves et al.(11) also supported our present study finding in which they stated a complete pathological response of 33.93%.

The analysis of histological regression patterns among patients reveals interesting, though not statistically significant, variations when stratified by gender, age group, and histological type. For gender, 6 male patients (27.3%) achieved a complete response, 1 (4.5%) showed no response, 13 (59.1%) exhibited a partial response, and 2 (9.1%) were not assessed. In comparison, 9 female patients (64.3%) had a complete response, 1 (7.1%) showed no response, and 4 (28.6%) demonstrated a partial response, with none unassessed. The p-value for gender was 0.11, suggesting no statistically significant difference in treatment response between males and females, despite the observed trends. When stratifying by age group, different patterns emerged: in the 18-40 years group, 1 patient (6.7%) achieved a complete response and 1 (5.9%) had a partial response. In the 41-50 years group, 5 patients (33.3%) achieved a complete response, and 3 (17.6%) had a partial response. The 51-60 years group saw the highest rates of complete response, with 7 patients (46.7%) achieving it, alongside 8 patients (47.1%) showing a partial response. In patients over 60 years, 2 (13.3%) had a complete response, and 5 (29.4%) had a partial response. The p-value for age group was 0.81, indicating no significant difference in histological regression across age groups. In the present study it was examined that how histological type influenced treatment response, comparing outcomes between patients with squamous cell carcinoma (SCC) and those with adenocarcinoma. Among the SCC patients, 10 (66.7%) achieved a complete histological response, indicating a strong treatment effect in this group. Additionally, 1 patient (50.0%) showed no response, 14 (82.4%) had a partial response, and 1 (50.0%) was not assessed. Conversely, in the adenocarcinoma group, only 5 patients (33.3%) achieved a complete response, suggesting the treatment was less effective for them. Similarly, 1 patient (50.0%) showed no response, 3 (17.6%) had a partial response, and 1 (50.0%) was not assessed. The p-value for histological type was 0.55, indicating no statistically significant difference in histological regression between SCC and adenocarcinoma. This suggests that within this study, histological type did not significantly influence treatment outcomes. However, the higher rate of complete response in

SCC compared to adenocarcinoma may still be of clinical interest, hinting at a trend that could be explored in further research.

The significant prevalence of squamous cell carcinoma in the second and third groups is consistent with existing research, which suggests a higher incidence of squamous cell carcinoma in certain populations and regions.(12) Additionally, the higher proportion of adenocarcinoma in the fourth group could reflect specific demographic or etiological factors that favor the development of adenocarcinoma over squamous cell carcinoma.(13) These observed variations may also suggest different risk factors or genetic predispositions influencing the histological outcomes of these tumors. This highlights the importance of these differences, indicating that the distribution of histological types is not random but likely influenced by underlying factors that require further investigation. Further investigation is necessary to confirm these findings and develop treatment approaches that consider the unique characteristics of each patient and the biology of the tumor.

Conclusion: Neoadjuvant concurrent chemoradiotherapy for patients with esophageal and gastroesophageal junction cancers shows considerable variability in pathological responses. In our study, 41.7% of patients achieved complete tumor regression, while others showed different degrees of response. These results highlight the treatment's effectiveness in reducing tumor burden and achieving significant downs taging in some patients. However, the variability in responses, influenced by factors such as gender, age and tumor resection underscores the need for further research. Future studies should focus on optimizing treatment protocols and developing personalized strategies to improve pathological responses and overall outcomes for patients with these complex malignancies.

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